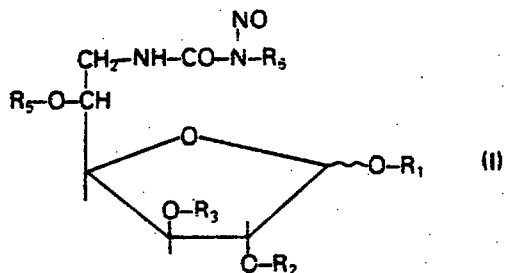


Glucofuranosid-6-yl-nitroso-urea derivatives, processes for their preparation and medicaments containing them

The invention relates to new N₁-glucofuranosid-6-yl-N₂-nitroso-ureas(sic) of the formula



wherein R₁ and R₂ represent hydrogen, alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen, or aralkyl or acyl which is optionally substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, and R₁ and R₂ together also represent alkylidene or cycloalkylidene, R₃ and R₅ denote alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen, or aralkyl or acyl which is optionally substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, and R₃ and R₅ together also denote alkylidene or cycloalkylidene, and R₆ denotes alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen.

In the text which follows, unless specially indicated, residues, radicals or compounds which are modified by the term "lower" contain up to 7, primarily up to 4, carbon atoms.

Alkyl is especially lower alkyl, for example isopropyl, linear or branched butyl, pentyl, hexyl or heptyl which is attached in any position and, above all, methyl, ethyl or n-propyl.

Suitable substituents of the optionally substituted alkyl group are primarily free or etherified hydroxyl groups, for example lower alkoxy groups, or halogen atoms. Moreover the substituted alkyl radical, such as a lower alkyl radical, can carry one, two or more identical or different substituents, in particular free hydroxyl groups or halogen atoms.

Aralkyl is especially aryl-lower alkyl wherein the lower alkyl moiety corresponds, above all, to the lower alkyl mentioned above and is primarily methyl or ethyl. The aromatic moiety is especially a monocyclic aryl radical, and also a bicyclic aryl radical, primarily phenyl, but also naphthyl. It can optionally be monosubstituted, disubstituted or polysubstituted, for example by lower alkyl groups, free or etherified hydroxyl, for example lower alkoxy or lower alkylenedioxy, halogen atoms and/or trifluoromethyl. 2-Phenylethyl, chlorobenzyl, methylbenzyl, hydroxybenzyl, methoxybenzyl or, above all, benzyl should be mentioned particularly.

The alkylidene radical is especially a lower alkylidene radical, such as the 2-butyldiene or 3-pentylidene radical and primarily the isopropylidene radical. The cycloalkylidene radical preferably contains 5 - 7 ring carbon atoms and is primarily cyclopentylidene or cyclohexylidene.

Acyl is especially an acyl radical of an organic acid, in particular an organic carboxylic acid. Thus acyl is especially alkanoyl, above all alkanoyl containing 2-18 carbon atoms, such as acetyl or propionyl, or aroyl, such as 1-naphthoyl, 2-naphthoyl and especially benzoyl or benzoyl or naphthoyl which is substituted by halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or lower alkanoyloxy. Acyl can also be an acyl radical of an organic sulfonic acid, for example an alkanesulfonic acid, especially a lower alkanesulfonic acid, such as methanesulfonic acid or ethane-

sulfonic acid, or an arylsulfonic acid, especially a phenyl-sulfonic acid which is optionally substituted by lower alkyl, such as benzenesulfonic acid or p-toluenesulfonic acid, and can also represent the radical of a carbamic acid, such as unsubstituted carbamoyl, lower alkylcarbamoyl or arylcarbamoyl, such as methylcarbamoyl or phenylcarbamoyl.

As a substituent of the abovementioned radicals, lower alkyl is primarily methyl or ethyl, but is also n-propyl, isopropyl or linear or branched butyl.

As a substituent of the abovementioned radicals, lower alkoxy is especially methoxy or ethoxy and also n-propoxy, isopropoxy, n-butoxy or isobutoxy.

Halogen is, for example, fluorine, chlorine or bromine.

The new compounds can exist in the form of mixtures of anomers or in the form of pure α -anomers or β -anomers.

The new compounds possess valuable pharmacological properties, in particular they exhibit a very good action in regard to certain transplantable tumours and leukaemias of various kinds, and also, in part, in regard to virus-induced leukaemia. Thus in doses of 25 - 500 mg/kg administered intraperitoneally they produce a considerable inhibition of tumour growth in mice having, for example, Ehrlich ascitic carcinoma or solid Harding-Passey melanoma and in the case of rats having, for example, Yoshida ascitic sarcoma. Analogous doses produced a prolongation of life compared with controls in the case of mice having, for example, L 1210 leukaemia or Rauscher leukaemia.

Thus an 800-100% (sic) inhibition in the growth of the said tumours and, in the case of L 1210 leukaemia, a prolongation of life of approx. 60 %, is achieved, for example, using ethyl-6-deoxy-3,5-di-O-methyl-6-(3-methyl-3-nitrosoureido)- β -D-glucofuranoside in doses of 50-250 mg/kg administered intraperitoneally, and also, after peroral administration, a prolongation of life of approx. 150 % in the case of mice having Rauscher leukaemia. The tolerance is good. Side effects are not observed even with prolonged

treatment. Nor can changes in organs be seen macroscopically in normal animals after peroral treatment for three weeks.

Sugar derivatives containing the nitrosourea group-
ing are known from the literature. Thus alkyl-N-carbamoyl-
N-2-chloroethyl-N'-nitroso-D-glucopyranosides are suggested
as tumour-inhibiting active compounds in Chemical Abstracts
85, 94652u (1976), and 5-nitrosoureido-5-deoxy-D-ribofuran-
ose derivatives are suggested as tumour-inhibiting active
compounds in Chemical Abstracts 86, 16911j (1977).

Compared with these, the compounds according to the
invention display a broad spectrum of action not only against
transplantable ascitic tumours (CrSa 180, Ehrlich carcinoma)
but also, above all, against various solid, transplantable
tumours or tumours induced by chemical means.

The invention relates especially to compounds of the
formula I wherein R_1 and R_2 denotes (sic) hydrogen, lower
alkyl which is optionally substituted by hydroxyl, lower
alkoxy or halogen or benzyl which is optionally substituted,
primarily in the para-position, by hydroxyl, lower alkoxy,
halogen or trifluoromethyl, and R_1 and R_2 also denote lower
alkylidene or cycloalkylidene having 5-6 carbon atoms, R_3
and R_5 denote lower alkyl which is optionally substituted
by hydroxyl, lower alkoxy or halogen, benzyl which is option-
ally substituted, primarily in the p-position, by hydroxyl,
lower alkoxy, halogen or trifluoromethyl, or lower alkanoyl,
for example acetyl or propionyl, or benzoyl which is option-
ally substituted by halogen, lower alkoxy, hydroxy or lower
alkanoyloxy, for example p-chlorobenzoyl, p-bromobenzoyl,
p-methoxybenzoyl, o-hydroxybenzoyl or p-hydroxybenzoyl, but
also together denote lower alkylidene or cycloalkylidene
having 5-6 carbon atoms, and R_6 denotes lower alkyl which
is optionally substituted by halogen, hydroxyl or lower
alkoxy.

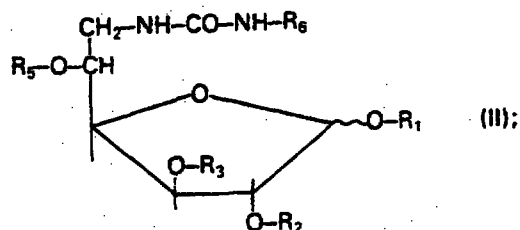
Compounds which are particularly valuable in this
respect are those in which R_3 and R_5 represent an identi-
cal radical.

Compounds of the above formula I which should be

singled out particularly are those wherein R_1 denotes lower alkyl and R_2 denotes hydrogen or R_1 and R_2 together denote lower alkylidene, R_3 and R_5 represent lower alkyl or benzyl which is optionally substituted, particularly in the p-position, by halogen, hydroxyl, lower alkoxy or alkyl, or R_6 represents lower alkyl which is optionally substituted by chlorine, for example methyl or chloroethyl.

Compounds which should be mentioned primarily are those wherein R_3 and R_5 denote methyl, R_6 denotes methyl or chloroethyl and R_1 denotes hydrogen, methyl, ethyl or propyl and R_2 denotes hydrogen, or R_1 and R_2 together denote the isopropylidene radical.

The new compounds are obtained if the nitroso group is introduced in a manner which is in itself known into a compound of the formula II



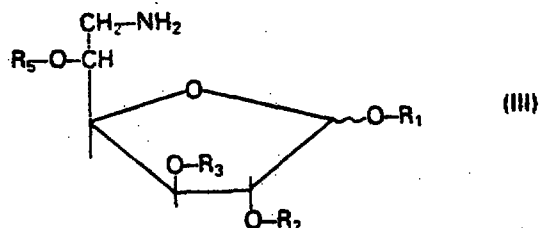
This is preferably effected by reacting the compound II with nitrous acid or salts or derivatives thereof. It is preferable to use for this purpose a salt, such as an alkali metal salt or alkaline earth metal salt, particularly the sodium salt, of nitrous acid and to liberate nitrous acid therefrom by means of an acid, such as a mineral acid, for example hydrochloric acid, sulfuric acid or nitric acid, an organic acid, such as carbonic acid, acetic acid or a sulfonic acid, for example a lower alkanesulfonic acid, such as methanesulfonic or ethanesulfonic acid, or an ion exchanger containing sulfonic acid groups, for example amberlite IR 120. However, it is also possible to use an anhydride of nitrous acid, in particular a mixed anhydride with, for example, nitric acid or a hydrogen halide acid.

If necessary the reaction is carried out in the presence of a solvent, in which case the solvent used can

also be, for example, an organic acid which is present. The reaction is preferably carried out at a low temperature, for example -10°C to 30°C .

The starting materials used in this process method are new. They can be obtained in a manner which is in itself known from a corresponding glucofuranose which is unsubstituted in the 6-position, for example by reacting the latter to give a reactive ester, for example an ester with an alkanesulfonic acid, arylsulfonic acid or hydrogen halide acid, and then reacting the product to give an azide and reducing the azide thus obtained to give 6-deoxy-6-amino-glucofuranose, which is then subjected to a condensation reaction with a suitable N-R₆-carbamic acid derivative, such as a corresponding isocyanate, to give 6-deoxy-6-(3-R₆-ureido)-glucofuranose. As mentioned above, these reactions are carried out in a manner which is in itself known.

A further method for the preparation of the new nitrosoureas consists in reacting a compound of the formula III



with a reactive derivative of an N-nitroso-N-R₆-carbamic acid (IV).

The reactive derivative can be, for example, an acid anhydride, preferably a mixed acid anhydride, such as an acid azide, or an activated ester. Activated esters which may be mentioned particularly are cyanomethyl esters, carboxymethyl esters, paranitrophenyl thioesters, paranitrophenyl esters, 2,4,5-trichlorophenyl esters, pentachlorophenyl esters, N-hydroxysuccinimide esters, N-hydroxyphthalimide esters, 8-hydroxyquinoline esters or N-hydroxypiperidine esters.

This reaction is carried out in a manner which is

in itself known, preferably in a solvent, such as water, a halogenated hydrocarbon, for example dichloroethane or trichloroethane, an ether, such as diethyl ether or tetrahydrofuran, dimethylformamide, dimethyl sulfoxide or an optionally alkylated pyridine, such as pyridine, picoline or lutidine, or quinoline.

The starting materials used are known or can be prepared in a manner which is in itself known. Thus the amine of the formula III can be obtained from a corresponding glucofuranose which is unsubstituted in the 6-position, for example by reacting the latter to give a reactive ester, for example an ester with an alkanesulfonic or arylsulfonic acid or with a hydrogen halide acid, and then reacting the product to give an azide and reducing the azide thus obtained to give 6-deoxy-6-aminoglucofuranose.

The processes described above are carried out by methods which are in themselves known, in the absence, or preferably in the presence, of diluents or solvents, if necessary with cooling or heating, under elevated pressure and/or in an inert atmosphere, for example under nitrogen.

The new compounds can exist as pure α -anomers or β -anomers or as mixtures of anomers. The latter can be separated into the two pure anomers on the basis of the physicochemical differences or constituents (sic) in a known manner, for example by chromatographic separation, such as thin layer chromatography, or any other suitable separation process. It is preferable to isolate the more active of the two anomers.

The invention also relates to those embodiments of the process in which a starting material is formed under the reaction conditions or is used in the form of a reactive derivative or salt. It is preferable to use as starting materials those which result, in accordance with the process, in the compounds described above as particularly valuable.

The present invention also relates to pharmaceutical formulations containing compounds of the formula I. The pharmaceutical formulations according to the invention are

formulations for enteral administration, such as oral and rectal administration, and also parenteral administration to warm-blooded animals and contain the pharmacological active compound on its own or together with a pharmaceutically usable excipient. The dosage of the active compound depends on the species of warm-blooded animal, its age and individual condition and on the mode of administration.

The new pharmaceutical formulations contain from about 10 % to about 95 %, preferably from about 20 % to about 90 %, of the active compound. Pharmaceutical formulations according to the invention can be in the form, for example, of unit dosage forms, such as coated tablets, tablets, capsules, suppositories or ampoules. The pharmaceutical formulations of the present invention are prepared in a manner which is in itself known, for example by conventional mixing, granulating, coating, dissolving or lyophilising processes.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose formulations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, maize, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and also carboxymethyl-starch, cross-linked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are primarily flow regulators and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Tablet cores are provided with suitable coatings, if appropriate coatings resistant to the gastric juices, using, inter alia, concentrated sugar solutions optionally containing gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, solutions of lacquers in suitable

organic solvents or mixtures of solvents, or, for the preparation of coatings resistant to the gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dye-stuffs or pigments, for example to identify or characterise different doses of active compound, can be added to the tablets or tablet coatings.

In the treatment of warm-blooded animals afflicted with tumours or leukaemia, in order to achieve tumour-inhibiting and/or leukaemia-inhibiting effects by administering a pharmaceutical formulation according to the invention, the daily dose for a warm-blooded animal weighing about 70 kg is about 10-500 mg per day, preferably 50-300 mg per day.

The examples which follow illustrate the invention described above; they are not, however, intended to limit the scope of the latter in any way. Temperatures are quoted in degrees centigrade.

Example 1

A solution of 15.8 g of sodium nitrite in 80 ml of water is added dropwise, in the course of 15 minutes, to a solution, cooled to 0°C, of 60.7 g of ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methylureido)- α -D-glucofuranoside in 500 ml of water and 15 ml of glacial acetic acid, the mixture is stirred for one hour at the same temperature and is allowed to stand at room temperature for 16 hours. The product which has crystallised out is filtered off with suction, washed with a little ice water and dried. The mother liquor is extracted with chloroform, the organic phase is dried over magnesium sulfate and the solvent is removed by distillation. The residue is purified by column chromatography over silica gel using 85:15 methylene chloride/ethyl acetate, the crystalline product is combined with the first crop of crystals, and the mixture is recrystallised from ether/petroleum ether. The ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranoside melts at 90°C; Rf value 0.45 on silica gel thin layer plates in the system

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methylene chloride/methanol (15:1); $[\alpha]_D^{20} = +43^\circ \pm 1^\circ$ (chloroform, $c = 1.465$).

The starting material can be prepared as follows:

67 ml of methanesulfonyl chloride are added dropwise, in the course of 45 minutes and with stirring and external cooling to a solution of 207 g of 3,5-di-O-methyl-1,2-O-isopropylidene- α -D-glucofuranose in 600 ml of absolute pyridine, and the mixture is allowed to stand at room temperature for 4 hours. 50 ml of water are then added and, after a further 15 minutes, the bulk of the pyridine is removed by evaporation. The residue is taken up in ether, the ethereal solution is washed with water, ice cold 2N hydrochloric acid, water, saturated sodium bicarbonate solution and water and is dried over magnesium sulfate, and the solvent is removed by distillation. The oily residue is 3,5-di-O-methyl-1,2-O-isopropylidene-6-O-mesyl- α -D-glucofuranose of Rf value 0.35 on silica gel thin layer plates in the system methylene chloride/ethyl acetate (85:15).

240 g of this product are dissolved in 1700 ml of N,N-dimethylformamide, 142 g of sodium azide and 170 ml of water are added, and the mixture is stirred at 110°C for 3 hours. The reaction mixture is cooled and filtered, and the filtrate is evaporated. The residue is taken up in ether, washed with water and dried over magnesium sulfate, and the solvent is removed by distillation. This gives 6-azido-6-deoxy-3,5-di-O-methyl-1,2-O-isopropylidene- α -D-glucofuranose in the form of a yellowing oil of Rf value 0.61 on silica gel thin layer plates in the system methylene chloride/ethyl acetate (85:15) and of optical rotation $[\alpha]_D^{20} = -57^\circ \pm 1^\circ$ (chloroform, $c = 1.915$).

A solution of 193 g of this compound in 3500 ml of 1N alcoholic hydrochloric acid is allowed to stand at room temperature for 18 hours. The bulk of the solvent is then removed by evaporation in a waterpump vacuum, the residue is taken up in ether, and this solution is washed with water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated to dryness. The resulting

mixture of anomers is separated by column chromatography over silica gel using 85:15 methylene chloride/ethyl acetate. The ethyl-6-azido-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside has an R_f value of 0.32 on silica gel thin layer plates in the system methylene chloride/ethyl acetate (85:15) and an optical rotation $[\alpha]_D^{20} = +56^\circ \pm 1^\circ$ (chloroform, c = 0.89). The corresponding β -glucofuranoside has an R_f value of 0.11 in the same system.

21.9 g of ethyl-6-azido-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside in 200 ml of ethanol are reduced with hydrogen in the presence of 2 g of 5 % strength palladium-on-charcoal. After filtering off the catalyst and removing the alcohol by distillation, ethyl-6-amino-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside is obtained in the form of a yellowish oil.

A solution of 18.5 ml of methyl isocyanate in 60 ml of methylene chloride are added dropwise, in the course of one hour, to a solution of 74.9 g of this oil in 550 ml of ethanol, and the reaction mixture is evaporated to dryness. The resulting ethyl-6-deoxy-3,5-di-O-methyl-6-(3-methylureido)- α -D-glucofuranoside is crystallised from ethyl acetate/ether; melting point 144° , $[\alpha]_D^{20} = +57^\circ \pm 1^\circ$ (chloroform, c = 1.134), and R_f value 0.22 on silica gel in the system methylene chloride/methanol (15.1).

Example 2

A solution of 8.5 g of sodium nitrite in 40 ml of water is added dropwise, in the course of 30 minutes, to a solution, cooled to 0-5°C, of 33.4 g of 3,5-D-O-methyl-6-deoxy-1,2-O-isopropylidene-6-(3-methylureido)- α -D-glucofuranose in 280 ml of water and 8.0 ml of glacial acetic acid. The mixture is stirred for one hour at 0.5° and for 18 hours at room temperature. The solution is then extracted with chloroform, and the organic phase is washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is chromatographed over 1200 g of silica gel using 85:15 methylene chloride/ethyl acetate. The fractions of R_f value 0.41 containing the 6-deoxy-3,5-di-O-methyl-1,2-O-

isopropylidene-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranose are evaporated to dryness; $[\alpha]_D^{20} = -49^\circ \pm 1^\circ$ (chloroform, $c = 1.127$).

The starting material used can be prepared as follows:

60.0 g of 6-azido-6-deoxy-3,5-di-O-methyl-1,2-O-isopropylidene- α -D-glucofuranose are dissolved in 600 ml of ethanol and reduced with hydrogen in the presence of 5 % strength palladium-on-charcoal. After removing the catalyst and distilling off the solvent, 6-amino-6-deoxy-3,5-di-O-methyl-1,2-O-isopropylidene- α -D-glucofuranose are obtained in the form of a colourless oil. 33.2 g of this product are dissolved in 250 ml of ethanol, and a solution of 8.4 ml of methyl isocyanate in 25 ml of methylene chloride is added dropwise, in the course of 30 minutes and with stirring. After being stirred for a further 60 minutes, the reaction mixture is evaporated to dryness, and the residue is crystallised from acetone. The 6-deoxy-3,5-di-O-methyl-1,2-O-isopropylidene-6-(3-methylureido)- α -D-glucofuranose thus obtained has an Rf value of 0.45 on silica gel in the system acetone and $[\alpha]_D^{20} = -57^\circ \pm 1^\circ$ (chloroform, $c = 1.987$) and melts at 66-69°.

Example 3

A solution of 25.4 g of sodium nitrite in 130 ml of water is added dropwise, in the course of 45 minutes and with stirring, to a solution, cooled to 0-5°C, of 52.4 g of ethyl-6-deoxy-3,5-di-O-methyl-6-(3-methylureido)- β -D-glucofuranoside in 420 ml of water and 24.5 ml of glacial acetic acid, and the mixture is stirred at the same internal temperature for 18 hours. It is then extracted with chloroform, and the organic phase is washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is chromatographed over silica gel using 85:15 methylene chloride/ethyl acetate. The fractions containing ethyl-6-deoxy-3,5-di-O-methyl-6-(3-methyl-3-nitrosoureido)- β -D-glucofuranoside, of Rf value 0.15, are combined and evaporated to dryness: $[\alpha]_D^{20} = -57^\circ \pm 1^\circ$ (chloroform, $c = 1.858$).

The starting material used can be prepared as follows:

24 g of ethyl-6-azido-6-deoxy-3,5-di-O-methyl- β -D-glucofuranoside are dissolved in 240 ml of methanol and reduced with hydrogen in the presence of 5 % strength palladium-on-charcoal. The catalyst is filtered off and the filtrate is evaporated to dryness. The resulting 6-amino derivative is used direct for further reaction.

A solution of 10 ml of methyl isocyanate in 30 ml of methylene chloride is added dropwise, in the course of 40 minutes and with stirring, to a solution of 39.2 g of the derivative in 330 ml of ethanol, and the mixture is allowed to stand at room temperature for 16 hours. The reaction mixture is then evaporated to dryness and the residue is taken up in ethyl acetate. This solution is filtered through active charcoal and evaporated to dryness. The resulting oil constitutes ethyl-6-deoxy-3,5-di-O-methyl-6-(3-methylureido)- β -D-glucofuranoside of Rf value 0.10 on silica gel in the system methylene chloride/methanol (15:1).

Example 4

The following compounds are obtained analogously, starting from the corresponding starting substances:

- a) Ethyl-2-O-acetyl-6-deoxy-3,5-O-methyl-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranoside, oil, $[\alpha]_D^{20} = +96^\circ \pm 1^\circ$ (chloroform, c = 0.710)
- b) Ethyl-6-(3-ethyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside, oil $[\alpha]_D^{20} = +41^\circ \pm 1^\circ$ (chloroform, c = 1.174)
- c) Ethyl-6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-3,5-di-O-methyl-D-glucofuranoside, oil, $[\alpha]_D^{20} = +37^\circ \pm 1^\circ$ (chloroform, c = 0.935)
- d) Ethyl-6-(3-n-butyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside, oil, $[\alpha]_D^{20} = +25^\circ \pm 1^\circ$ (chloroform, c = 1.579)
- e) Ethyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)-3-O-propyl- α -D-glucofuranoside, melting point = 41° , $[\alpha]_D^{20} = +37^\circ \pm 1^\circ$ (chloroform, c = 0.926)

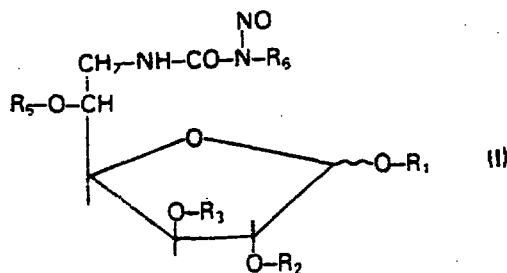
- f) Ethyl-5-O-ethyl-6-deoxy-6-(3-methyl-3-nitrosoureido)-3-O-propyl- α -D-glucofuranoside, melting point = 60° , $[\alpha]_D^{20} = 28^{\circ} \pm 1^{\circ}$ (chloroform, $c = 1.362$) and
- g) Ethyl-3-O-benzyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranoside, melting point = $92-93^{\circ}$, $[\alpha]_D^{20} = +32^{\circ} \pm 1^{\circ}$ (chloroform, $c = 1.438$).

Example 5

A solution of 2.5 g of N-nitrosomethylcarbamoyl azide in 40 ml of ether is added dropwise, in the course of 10 minutes and with stirring, to a solution, cooled to 0°C , of 5.0 g of ethyl-6-amino-6-deoxy-3,5-di-O-methyl- α -D-glucofuranoside in 40 ml of chloroform, and stirring is continued for a further hour in an ice bath and for 3 hours at room temperature. The solution is then concentrated to one half, washed with ice cold 2N hydrochloric acid, water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated to dryness. The crystalline residue of ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranoside is recrystallised from ether/petroleum ether: melting point 90°C , $[\alpha]_D^{20} = +43^{\circ} \pm 1^{\circ}$ (chloroform, $c = 1.102$).

Patent Claims

1. N_1 -Glucofuranosid-6-yl- N_3 -nitrosoureas of the formula



wherein R_1 and R_2 represent hydrogen, alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen, or aralkyl or acyl which is optionally substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, and R_1 and R_2 together also represent alkylidene or cycloalkylidene, R_3 and R_5 denote alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen, or aralkyl or acyl which is optionally substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, and R_3 and R_5 together also denote alkylidene or cycloalkylidene, and R_6 denotes alkyl which is optionally substituted by free or etherified hydroxyl groups or by halogen.

2. Compounds according to claim 1, wherein R_1 and R_2 denote hydrogen, lower alkyl which is optionally substituted by hydroxyl, lower alkoxy or halogen, or benzyl which is optionally substituted by hydroxyl, lower alkoxy, halogen or trifluoromethyl, or R_1 and R_2 also denote lower alkylidene or cycloalkylidene having 5-6 carbon atoms, R_3 and R_5 denote lower alkyl which is optionally substituted by hydroxyl, lower alkoxy or halogen, benzyl which is optionally substituted by hydroxyl, lower alkoxy, halogen or trifluoromethyl, lower alkanoyl, or benzoyl which is optionally substituted by halogen, lower alkoxy, hydroxyl or lower alkanoyloxy, but also together denote lower alkylidene or cycloalkylidene having 5-6 carbon atoms, and R_6 is a lower alkyl radical which is optionally substituted by halogen, hydroxyl or lower alkoxy.

3. Compounds according to claim 2, wherein the substituted benzyl radical is substituted in the para-position.
4. Compounds according to claim 1, wherein R_1 denotes lower alkyl and R_2 denotes hydrogen or R_1 and R_2 together denote lower alkylidene, R_3 and R_5 represent lower alkyl, or benzyl which is optionally substituted by halogen, hydroxyl, lower alkoxy or alkyl, and R_6 represents lower alkyl which is optionally substituted by chlorine.
5. Compounds according to claim 1, wherein R_1 denotes hydrogen, methyl, ethyl or propyl and R_2 denotes hydrogen and R_1 and R_2 together denote the isopropylidene radical and R_3 and R_5 represent methyl and R_6 represents methyl or chloroethyl.
6. The α -anomers or β -anomers of the compounds mentioned in patent claims 1-5.
7. Ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methyl-3-nitroso-ureido)- α -D-glucofuranoside or ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methyl-3-nitrosoureido)- β -D-glucofuranoside.
8. 6-Deoxy-3,5-di-O-methyl-1,2-O-isopropylidene-6-(3-methyl-3-nitrosoureido)- α -D-glucofuranose.
9. Ethyl-2-O-acetyl-6-deoxy-3,5-di-O-methyl-6-(3-methyl-3-nitrosoureido)-D-glucofuranoside.
10. Ethyl-6-(3-ethyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl-D-glucofuranoside.
11. Ethyl-6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-3,5-di-O-methyl-D-glucofuranoside.
12. Ethyl-6-(3-n-butyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl-D-glucofuranoside.
13. Ethyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)-3-O-propyl-D-glucofuranoside.
14. Ethyl-5-O-ethyl-6-deoxy-6-(3-methyl-3-nitrosoureido)-3-O-propyl-D-glucofuranoside.
15. Ethyl-3-O-benzyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)-D-glucofuranoside.
16. Pharmaceutical formulations containing one of the compounds mentioned in claims 1 to 15.
17. Compounds according to claim 1 for use in a process

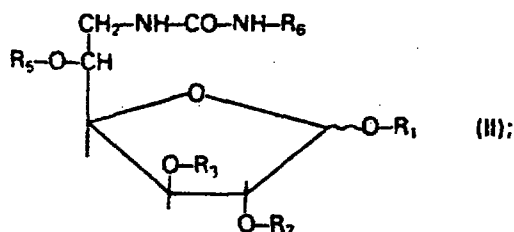
for the therapeutic treatment of the human body or of an animal body.

18. Compounds according to claim 1 as tumour-inhibiting agents.

19. The use of compounds according to claim 1 for the preparation of pharmaceutical formulations.

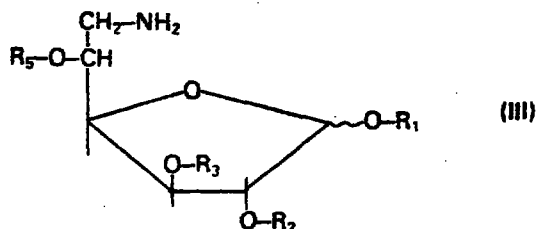
20. Process for the preparation of N₁-glucofuranosid-6-yl-N₃-nitrosoureas according to claim 1, characterised in that, in a manner which is in itself known,

a) the nitroso group is introduced into a compound of the formula



or

b) an amine of the formula



is subjected to a condensation reaction with a reactive derivative of an N-nitroso-N-R₆-carbamic acid (IV).

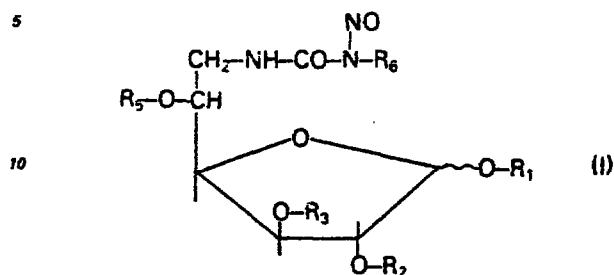
21. Compounds which can be obtained by the processes of claim 20.



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Claims

1. N₁-Glucufuranosid-6-yl-N₃-nitroso-ureas of the formula I



wherein R₁ and R₂ are each hydrogen, alkyl which is unsubstituted or substituted by free or etherified hydroxyl groups or halogen, or they are each aralkyl or acyl which are each unsubstituted or substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, or R₁ and R₂ together are also alkylidene or cycloalkylidene, R₃ and R₅ are each alkyl which is unsubstituted or substituted by free or etherified hydroxyl groups or halogen, or they are each aralkyl or acyl which are each unsubstituted or substituted by lower alkyl, free or etherified hydroxyl, halogen or trifluoromethyl, or R₃ and R₅ together are also alkylidene or cycloalkylidene, and R₆ is alkyl which is unsubstituted or substituted by free or etherified hydroxyl groups or halogen.

2. Compounds according to Claim 1, wherein R₁ and R₂ are each hydrogen, lower alkyl which is unsubstituted or substituted by hydroxyl, lower alkoxy or halogen, or they are each benzyl which is unsubstituted or substituted by hydroxyl, lower alkoxy, halogen or trifluoromethyl, or R₁ and R₂ together are also lower alkylidene or cycloalkylidene having 5-6 carbon atoms, R₃ and R₅ are each lower alkyl which is unsubstituted or substituted by hydroxyl, lower alkoxy or halogen, or they are each benzyl which is unsubstituted or substituted by hydroxyl, lower alkoxy, halogen or trifluoromethyl, or they are each lower alkanoyl, or benzoyl which is unsubstituted or substituted by halogen, lower alkoxy, hydroxyl or lower alkanoyloxy, or together they are also lower alkylidene or cycloalkylidene having 5-6 carbon atoms, and R₆ is a lower alkyl group which is unsubstituted or substituted by halogen, hydroxyl or lower alkoxy.

3. Compounds according to Claim 2, wherein the substituted benzyl group is substituted in the para-position.

4. Compounds according to Claim 1, wherein R₁ is lower alkyl and R₂ is hydrogen, or R₁ and R₂ together are lower alkylidene, R₃ and R₅ are each lower alkyl, or benzyl which is unsubstituted or substituted by halogen, hydroxyl, lower alkoxy or alkyl, and R₆ is lower alkyl which is unsubstituted or substituted by chlorine.

5. Compounds according to Claim 1, wherein R₁ is hydrogen, methyl, ethyl or propyl, and R₂ is hydrogen, or R₁ and R₂ together are the isopropylidene group, and R₃ and R₅ are each methyl, and R₆ is methyl or chloroethyl.

6. The α - or β -anomers of the compounds stated in Claims 1-5.

7. Ethyl-3,5-di-O-methyl-6-deoxy-6-(3-methyl-3-nitrosoureido)- α -D-glucufuranoside or β -D-glucufuranoside.

8. 6-Deoxy-3,5-di-O-methyl-1,2-O-isopropylidene-6-(3-methyl-3-nitrosoureido)- α -D-glucufuranose.

9. Ethyl-2-O-acetyl-6-deoxy-3,5-di-O-methyl-6-(3-methyl-3-nitrosoureido)-D-glucufuranoside.

10. Ethyl-6-(3-ethyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl-D-glucufuranoside.

11. Ethyl-6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-3,5-di-O-methyl-D-glucufuranoside.

12. Ethyl-6-(3-n-butyl-3-nitrosoureido)-6-deoxy-3,5-di-O-methyl-D-glucufuranoside.

13. Ethyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)-3-O-propyl-D-glucufuranoside.

14. Ethyl-5-O-ethyl-6-deoxy-6-(3-methyl-3-nitrosoureido)-3-O-propyl-D-glucufuranoside.

15. Ethyl-3-O-benzyl-6-deoxy-5-O-methyl-6-(3-methyl-3-nitrosoureido)-D-glucufuranoside.

16. Pharmaceutical preparations containing one of the compounds given in Claims 1 to 15.

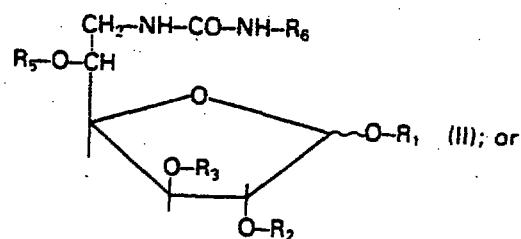
17. Compounds according to Claim 1 for application in a process for the therapeutic treatment of the human or animal body.

18. Compounds according to Claim 1 as active substances inhibiting tumors.

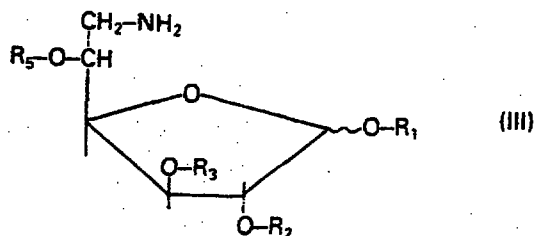
19. The use of compounds according to Claim 1 for the production of pharmaceutical preparations.

20. A process for producing N₁-glucufuranosid-6-yl-N₃-nitroso-ureas according to Claim 1, which process comprises

a) introducing the nitroso group, in a manner known per se, into a compound of the formula



b) condensing, in a manner known per se, an amine of the formula



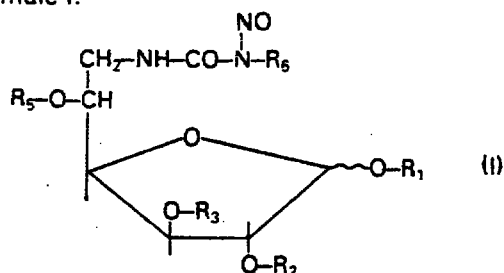
with a reactive derivative of an N-nitroso-N-R₆-carbamic acid (IV).

21. The compounds obtainable by the process according to Claim 20.



Revendications

1. N₁-glucofurannoside-6-yl-N₃-nitroso-urées de formule I:



dans laquelle R₁ et R₂ représentent l'hydrogène, un groupe alkyle éventuellement substitué par des groupes hydroxy libres ou étherifiés ou par des halogènes ou un groupe aralkyle ou acyle éventuellement substitué par des groupes alkyle inférieurs, hydroxy libre ou étherifié, des halogènes ou des groupes trifluorométhyle, R₃ et R₄ représentent également ensemble un groupe alkylidène ou cycloalkylidène, R₄ et R₅ représentent un groupe alkyle éventuellement substitué par des groupes hydroxy libres ou étherifiés ou par des halogènes ou un groupe aralkyle ou acyle éventuellement substitué par des groupes alkyles inférieurs, hydroxy libre ou étherifié, des halogènes ou des groupes trifluorométhyle, R₃ et R₅ représentent également ensemble un groupe alkylidène ou cycloalkylidène, et R₆ représente un groupe alkyle éventuellement substitué par des groupes hydroxy libres ou étherifiés ou par des halogènes.

2. Composés selon la revendication 1, dans lesquels R₁ et R₂ représentent l'hydrogène, un groupe alkyle inférieur éventuellement substitué par des groupes hydroxy, alcoxy inférieur ou des halogènes, un groupe benzyle éventuellement substitué par des groupes hydroxy, alcoxy inférieur, des halogènes ou des groupes trifluorométhyle, R₃ et R₄ représentent également un groupe alkylidène inférieur ou cycloalkylidène en C5 - C6, R₃ et R₅ représentent un groupe alkyle inférieur éventuellement substitué par des groupes hydroxy, alcoxy inférieur ou des halogènes, un groupe benzyle éventuellement substitué par des groupes hydroxy, alcoxy inférieur, des halogènes, ou des groupes trifluorométhyle, un groupe alcanoyloxy inférieur ou un groupe benzoyloxy éventuellement substitué par des halogènes, des groupes alcoxy inférieur, hydroxy ou alcanoyloxy inférieur, ou représentent ensemble un groupe alkylidène inférieur ou cycloalkylidène en C5 - C6, et R₆ représente un groupe alkyle inférieur éventuellement substitué par des halogènes, des groupes hydroxy ou alcoxy inférieur.

3. Composés selon la revendication 2, dans lesquels le groupe benzyle substitué est substitué en position para.

4. Composés selon la revendication 1, dans lesquels R₁ représente un groupe alkyle inférieur et R₂ l'hydrogène ou bien R₁ et R₂ représentent ensemble un groupe alkylidène inférieur, R₃ et R₅ représentent un groupe alkyle inférieur ou un

groupe benzyle éventuellement substitué par des halogènes, des groupes hydroxy, alcoxy inférieur ou alkyle et R₆ représente un groupe alkyle inférieur éventuellement substitué par le chlore.

5. Composés selon la revendication 1, dans lesquels R₁ représente l'hydrogène, un groupe méthyle, éthyle ou propyle et R₂ représente l'hydrogène, et R₃ et R₄ représentent ensemble le reste isopropylidène et R₅ et R₆ représentent un groupe méthyle et R₆ un groupe méthyle ou chloréthyle.

6. Les anomères alpha ou bêta des composés mentionnés dans les revendications 1 à 5.

7. L'éthyl-3,5-di-O-méthyl-6-désoxy-6-(3-méthyl-3-nitrosouréido)-alpha-D-glucofurannoside ou -bêta-D-glucofurannoside.

8. Le 6-désoxy-3,5-di-O-méthyl-1,2-O-isopropylidène-6-(3-méthyl-3-nitroso-uréido)-alpha-D-glucofurannoside.

9. L'éthyl-2-O-acétyl-6-désoxy-3,5-di-O-méthyl-6-(3-méthyl-3-nitrosouréido)-D-glucofurannoside.

10. L'éthyl-6-(3-éthyl-3-nitrosouréido)-6-désoxy-3,5-di-O-méthyl-D-glucofurannoside.

11. L'éthyl-6-[3-(2-chloréthyl-3-nitrosouréido)]-6-désoxy-3,5-di-O-méthyl-D-glucofurannoside.

12. L'éthyl-6-(3-n-butyl-3-nitrosouréido)-6-désoxy-3,5-di-O-méthyl-D-glucofurannoside.

13. L'éthyl-6-désoxy-5-O-méthyl-6-(3-méthyl-3-nitrosouréido)-3-O-propyl-D-glucofurannoside.

14. L'éthyl-5-O-éthyl-6-désoxy-6-(3-méthyl-3-nitrosouréido)-3-O-propyl-D-glucofurannoside.

15. L'éthyl-3-O-benzyl-6-désoxy-5-O-méthyl-6-(3-méthyl-3-nitrosouréido)-D-glucofurannoside.

16. Compositions pharmaceutiques contenant l'un des composés mentionnés dans les revendications 1 à 15.

17. Composés selon la revendication 1, pour l'utilisation dans un procédé pour le traitement

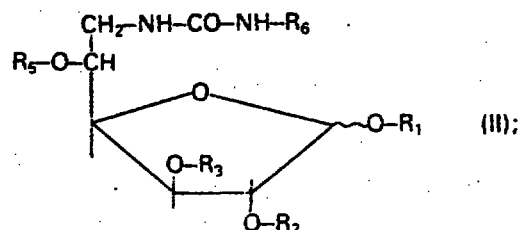
thérapeutique de l'organisme humain ou animal.

18. Composés selon la revendication 1, en tant qu'agents inhibiteurs des tumeurs.

19. Utilisation des composés selon la revendication 1 pour la préparation de compositions pharmaceutiques.

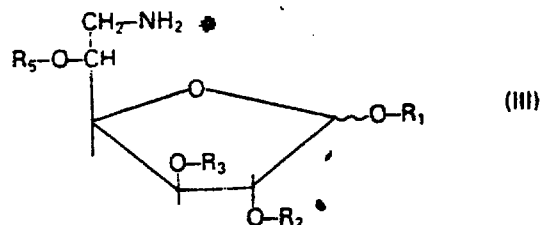
20. Procédé de préparation des N₁-glucofurannoside-6-yl-N₃-nitrosourées selon la revendication 1, caractérisé en ce que, de manière connue en soi:

a) on nitrose un composé de formule:



ou bien

b) on condense une amine de formule:



avec un dérivé réactif d'un
 acide N-nitroso-N-R₆-carbamique (IV)
 21. Composés susceptibles d'être obtenus par le
 procédé de la revendication 20.